



NOTES

NORMOCYTIC ANEMIA (INCREASED HEMOLYSIS)

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Inherited/acquired disorders resulting in premature destruction of normal red blood cells (RBCs)

SIGNS & SYMPTOMS

- If hematopoietic compensation insufficient, anemic symptoms (e.g. pallor, fatigue, activity intolerance)
- Intravascular hemolysis → hemoglobinuria, iron deficiency
- Extravascular hemolysis → jaundice, splenomegaly, gallstone formation

DIAGNOSIS

LAB RESULTS

- Complete blood count (CBC)
- Peripheral blood smear analysis
- Measure plasma for hemolysis indicators
 - Bilirubin, lactate dehydrogenase (LDH), haptoglobin
- Measure specific indicators of hemolysis in urine
 - Hemoglobin, bilirubin, hemosiderin

TREATMENT

- See individual disorders

AUTOIMMUNE HEMOLYTIC ANEMIA (AHA)

osms.it/autoimmune-hemolytic-anemia

PATHOLOGY & CAUSES

- Anemia caused by immune **destruction of red blood cells** by autoantibodies against antigens on RBCs surface
- **AKA AIHA**

TYPES

Warm AIHA

- Most common
- “Warm” because **optimum temperature** for antibody to react with RBCs = normal body

temperature (37°C/98.6°F)

- **Predominant autoantibody:** IgG (IgA and IgM may also be involved)
- **Predominant RBC antigen:** Rh
- Associated with immune deficiencies, malignancies, certain drugs
- Antibody fixes complement + binds to RBC membrane → antibody-coated RBCs destroyed in spleen
 - **Usual site of hemolysis:** extravascular, by macrophages in spleen, liver

VISIT...

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Cold AIHA

- “Cold” because optimum temperature for antibody to react with RBCs = below normal body temperature (4°C/39.2°F)
- Predominant autoantibody: IgM
- Predominant RBC antigen: I, i, P
- Antibodies activate direct complement system attack
- Usual site of hemolysis: intravascular, complement-mediated
- Paroxysmal cold hemoglobinuria
 - Most common in children
 - Caused by Donath–Landsteiner antibody
 - Associated with viral (e.g. measles, varicella) or bacterial (e.g. mycoplasma, *H. influenza*) infections
- Cold agglutinin syndrome
 - Most common in adults > 70 years old
 - Primarily biologically-female individuals
 - Associated with lymphoproliferative disorders, autoimmune disorders, mycoplasma infections

AUTOIMMUNE HEMOLYTIC ANEMIA CLASSIFICATIONS

WARM	COLD
PRIMARY: Idiopathic	ACUTE: Infections
SECONDARY: Chronic autoimmune disease, B-cell neoplasms, infections, medications	CHRONIC: Idiopathic; B-cell neoplasms

RISK FACTORS

- Exposure to cold
- Administration of offending drug
- Development of associated diagnosis
 - Infection, malignancy, autoimmune disorder

COMPLICATIONS

- Depend on type/degree of hemolysis
- Anemia, venous thromboembolism, cholelithiasis, renal insufficiency
- Older individuals: increased risk of cardiac complications

SIGNS & SYMPTOMS

- Onset insidious/acute
- If hematopoietic compensation insufficient, anemic signs and symptoms (e.g. pallor, fatigue, activity intolerance)
- If severe anemia/underlying cardiac disease, a hyperdynamic state (e.g. bounding pulses, tachycardia, pulmonary congestion)
- Cold AIHA
 - Hemoglobinuria after exposure to cold temperatures
- Paroxysmal cold hemoglobinuria
 - Jaundice, hemoglobinuria, anemia after infection; pain in legs, back following exposure to cold
- Cold agglutinin syndrome
 - Anemia, acrocyanosis, or Raynaud's phenomenon

DIAGNOSIS

LAB RESULTS

- Evidence of hemolysis
 - Increased lactate dehydrogenase (LDH)
 - Increased indirect bilirubin
 - Decreased haptoglobin
- Increased mean corpuscular volume (MCV)
- Low hemoglobin, hematocrit
- Reticulocytosis
- Direct antibody (DAT)
 - Warm: positive for IgG/IgG + C3d
 - Cold: positive for C3d
- Partial macrophage phagocytosis → spherocytosis

TREATMENT

- Cold AIHA: often no treatment required

MEDICATIONS

- Corticosteroids
- Monoclonal antibody: rituximab
- Immunosuppressants

SURGERY

- Splenectomy (reduces hemolysis)

OTHER INTERVENTIONS

- Eliminate triggers (e.g. cold, drugs)
- Correct anemia
 - Folic acid supplements to support erythropoiesis
 - Blood transfusion

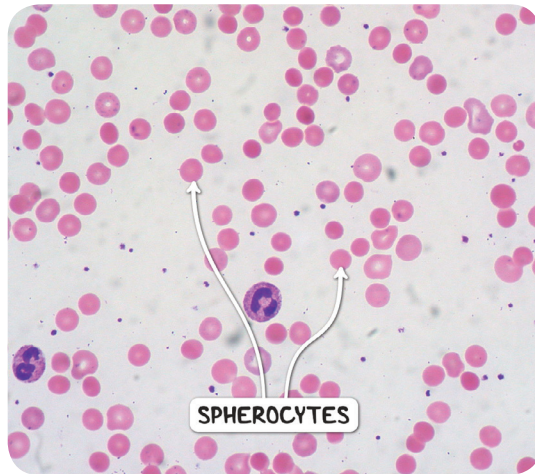


Figure 54.1 A peripheral blood smear from an individual with warm autoimmune hemolytic anemia. There are numerous spherocytes present due to degradation of the red cell membrane by macrophages.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

osms.it/G6PD

PATHOLOGY & CAUSES

- Hematological enzymopathy where deficient glucose-6-phosphate dehydrogenase (G6PD) causes **premature hemolysis**
- Inherited, X-linked mutation of G6PD gene
- Hemolysis can be acute/intermittent/chronic (rare)
- Inadequate G6PD, GSH → oxidative stress → **build-up of free radicals, peroxides** → precipitation of hemoglobin → disruption of cell membrane → increased cellular rigidity → extravascular hemolysis, **accelerated removal of damaged RBCs** by reticuloendothelial system in spleen; intravascular hemolysis may also occur
- Hemolysis precipitated by sources of oxidative damage that trigger hemolysis.
 - RBCs with deficient G6PD have a decreased lifespan
 - **Certain drugs** (sulfa drugs, antimalarials) and **chemicals** (e.g. henna compounds, aniline-based dyes, naphthalene) interact with hemoglobin + oxygen → hydrogen peroxide (H_2O_2), other oxidizing radicals within cell → hemoglobin precipitation
 - Infections → possible generation of hydrogen peroxide by leukocytes/exposure to neutrophil produced oxidants → hemoglobin precipitation
 - **Ingestion of fava beans (favism)**

W.H.O. Classifications

- Based on degree of enzyme deficiency, resulting hemolysis
- **Class I:** G6PD < 10% of normal; chronic hemolytic anemia
- **Class II:** G6PD < 10% of normal; intermittent hemolysis when exposed to

oxidative stress

- **G6PD Mediterranean**: majority of RBCs hemolyze in setting of oxidative stress; half-life of G6PD especially short (measured in hours)
- **Class III**: G6PD 10–60% of normal; intermittent hemolysis when exposed to trigger
 - **G6PD A-** : only oldest RBCs hemolyze in setting of oxidative stress; G6PD half-life = 13 days (normal = 62 days)

TYPES

- Acute hemolysis
 - May be mild/severe (life-threatening)
- Kernicterus
 - G6PD-related neonatal jaundice → kernicterus if not promptly treated
- Renal failure

RISK FACTORS

- Most common in people of African, Asian, Mediterranean descent

SIGNS & SYMPTOMS

- Generally asymptomatic until exposed to oxidative stress
- Acute hemolysis
 - Pallor, jaundice, dark urine
 - **Abdominal/back pain** due to increased splenic activity
 - **Renal insufficiency** (severe hemolysis)
- Favism (potentially fatal acute hemolysis)

DIAGNOSIS

LAB RESULTS

- Decreased hemoglobin
- Heinz bodies
 - Caused by precipitation of oxidized, denatured hemoglobin
- Bite cells
 - Cells have bitten appearance where macrophages have removed bits of precipitated hemoglobin from RBC
- Blood chemistry demonstrates evidence of hemolysis

- Elevated indirect bilirubin
- Elevated lactate dehydrogenase (LDH)
- Decreased haptoglobin

- Reticulocytosis
- Hemoglobinuria, hemosiderinuria
- G6PD assay
 - Directly measures G6PD activity in RBCs; false-negative if testing done during/immediately after acute hemolytic episode
- Screening tests
 - **Fluorescent spot test**: glucose-6-phosphate + NADP added to hemolysate of individual's RBCs → fluorescence of NADPH
 - **Methemoglobin reduction test**: methylene blue measures transfer of hydrogen ions from NADPH to methemoglobin → indirectly estimates NADPH generation
 - **Newborn screening**: blood analyzed for biochemical, genetic markers of G6PD, other inherited disorders
- Confirmatory test to assay NADPH formation performed after positive screening test/as initial test
 - Spectrophotometric analysis of RBC hemolysate + glucose-6-phosphate + NADP measures NADPH generation rate

TREATMENT

MEDICATIONS

- Folic acid supplements (support erythropoiesis)

OTHER INTERVENTIONS

- Eliminate triggers
- Manage acute hemolytic episodes
 - Hydration
 - Transfusions
- Phototherapy, exchange transfusion
 - Neonatal jaundice

HEMOLYTIC DISEASE OF THE NEWBORN

osms.it/hemolytic-disease-of-the-newborn

PATHOLOGY & CAUSES

- Anemia caused by **hemolytic destruction** of fetal/neonatal erythrocytes **by maternal antibodies**
- AKA alloimmune HDFN/erythroblastosis fetalis

CAUSES

- Fetomaternal hemorrhage **exposes maternal circulation to antigens** present on fetal RBCs → maternal sensitization → formation of maternal IgG antibodies against fetal RBCs → IgG antibodies small enough to cross placenta → antibody attachment to fetal cells → agglutination (clumping) → microcirculatory impairment → hemolysis, **destruction of RBCs by macrophages** in reticuloendothelial system
 - Involves Rhesus (Rh) blood group/A, B, AB, O blood groups
- Causes of maternal sensitization include normal delivery, spontaneous/induced abortion, chorionic villus sampling, amniocentesis, antenatal hemorrhage, maternal trauma, idiopathic
 - Small amount (0.1mL) of fetal blood needed to induce maternal immune response
- Rh incompatibility
 - **Rh negative mother exposed to Rh positive fetal RBCs** → maternal anti-D antibodies formed
 - Usually will not affect first pregnancy when initial exposure occurs; **adversely affects subsequent pregnancies**
 - Decreasing occurrence due to availability of Rh(D) immune globulin prophylaxis
- ABO incompatibility
 - More common, less severe morbidity, mortality than with Rh incompatibility

- Occurs in **type O mother** with naturally-occurring Anti-A and Anti-B antibodies + **Type A/Type B fetus**
- Can occur in **first and all subsequent pregnancies**

RISK FACTORS

- Blood group incompatibility, fetomaternal hemorrhage

COMPLICATIONS

- Anemia, hyperbilirubinemia, kernicterus
- Growth restriction, hydrops fetalis, erythroblastosis fetalis
 - Increased immature RBCs in fetal circulation

SIGNS & SYMPTOMS

- Hemolytic disease caused by ABO incompatibility
 - Mild to moderate hyperbilirubinemia within first 24h of life
 - Mild to moderate anemia
- Hemolytic disease caused by Rh incompatibility (more severe)
 - **Hyperbilirubinemia, kernicterus:** possible
 - **Symptomatic anemia:** pallor, lethargy, tachycardia, tachypnea
 - **Hydrops fetalis:** related to severe anemia-induced hypoxia; subcutaneous edema, pleural/pericardial effusion, ascites, signs and symptoms of shock
- Antenatal presentation
 - Intrauterine growth restriction signals problems with ongoing hemolysis, hypoxia

DIAGNOSIS

DIAGNOSTIC IMAGING

Doppler ultrasound

- Antenatal (maternal testing)
- Notes growth restriction/presence of hydrops

LAB RESULTS

- Antenatal (maternal testing)
 - **Positive indirect antiglobulin test: IAT, indirect Coombs test;** demonstrates IgG antibodies in maternal serum
 - **Kleihauer–Betke test:** positive if fetomaternal hemorrhage has occurred
 - **Percutaneous umbilical blood sampling (PUBS):** measures hemoglobin, hematocrit, identifies fetal blood type
 - **Spectrophotometric amniotic fluid analysis:** increased bilirubin if significant hemolysis has occurred
- Postnatal (neonatal testing)
 - **Blood typing:** confirm **incompatibility of** maternal, neonatal **blood types**
 - **Positive direct antiglobulin test:** DAT, direct Coombs test; evidence of maternal antibodies on RBC surface
 - **Positive indirect antiglobulin test:** IAT, indirect Coombs test; evidence of maternal antibodies in serum
 - **Transcutaneous bilirubin (TcB), serum bilirubin:** increased
 - **CBC:** decreased RBCs, reticulocytosis, decreased hemoglobin and hematocrit
 - **Peripheral blood smear analysis:** evidence of hemolysis; polychromasia, microspherocytosis (seen in ABO incompatibility)

TREATMENT

MEDICATIONS

- Hematopoietic agents (epoetin alfa/darbepoetin), iron supplements
 - Anemia

OTHER INTERVENTIONS

- RBC transfusion
 - Anemia, hydrops fetalis
- Exchange transfusion
 - Hyperbilirubinemia, hydrops fetalis
- Phototherapy
 - Hyperbilirubinemia
- Intravenous immunoglobulin (IVIG)
 - Hyperbilirubinemia
 - Reduces hemolysis, bilirubin production
- Pericardiocentesis, paracentesis, thoracentesis
 - Hydrops fetalis; as indicated for pericardial effusion, pleural effusion, ascites
- Intrauterine RBC transfusion
 - Hydrops fetalis if diagnosed antenatally

HEREDITARY SPHEROCYTOSIS

osms.it/hereditary-spherocytosis

PATHOLOGY & CAUSES

- Inherited RBC membrane defect causing destabilization of cellular membrane, resulting in **chronic, premature extravascular hemolysis**
- Autosomal dominant (75%) or autosomal recessive (25%)
- **Mutations of genes** encoding for proteins that secure RBC membrane skeleton to plasma membrane → **membrane destabilization** → rigidity, resistance to deformability → **hemolysis**

TYPES

Mild (20–30%)

- Mild anemia, splenomegaly, jaundice; modest reticulocytosis; normal hemoglobin
- Adolescents/adults most commonly diagnosed

Moderate (60–70%)

- Moderate anemia, reticulocytosis, hyperbilirubinemia
- Require occasional transfusions
- Infants/children most commonly diagnosed

Severe (5%)

- Marked anemia, hyperbilirubinemia, splenomegaly
- Regular transfusions needed

RISK FACTORS

- Most common in people of Northern European descent

COMPLICATIONS

- **Transient aplastic crisis** caused by infections (e.g. parvovirus B19)
- Megaloblastic anemia related to folate deficiency
- Neonatal icterus; non-immune hydrops fetalis with fetal death if disease = severe

SIGNS & SYMPTOMS

- Jaundice
- Anemic signs and symptoms (e.g. pallor, fatigue, activity intolerance)
- **Splenomegaly**

DIAGNOSIS

LAB RESULTS

- Decreased hemoglobin
- Reticulocytosis
- Spherocytosis
 - Morphology = sphere-shaped (normal = biconcave)
- Presence of schistocytes (RBC fragments)
- **Slightly decreased to normal MCV**
 - **Spherocytes:** **decreased MCV**
 - **Reticulocytes:** **increased MCV**
- Elevated mean cell hemoglobin concentration (MCHC)
 - Secondary to dehydration, **loss of cellular membrane**
- Elevated red cell distribution width (RDW)
- Evidence of hemolysis
 - Elevated indirect bilirubin
 - Elevated lactate dehydrogenase (LDH)
 - Decreased haptoglobin
- Osmotic fragility test, acidified glycerol lysis test (AGLT)
 - Identifies spherocytes which **lyse in hypotonic solutions** at higher rate than normal RBCs
- Cryohemolysis test
 - Uses hypertonic solution, temperature manipulation to identify spherocytes which lyse at higher rate than normal RBCs
- Eosin-5-maleimide (EMA) binding test
 - Flow cytometric test to observe cell membrane protein interaction with eosin-5-maleimide dye

- Osmotic gradient ektacytometry
 - Measures surface area to volume, cell hydration, membrane deformability

TREATMENT

SURGERY

- Splenectomy

OTHER INTERVENTIONS

- Blood transfusions
- Phototherapy, exchange transfusions
 - Neonatal hyperbilirubinemia
- Folic acid supplements
 - Support hematopoiesis

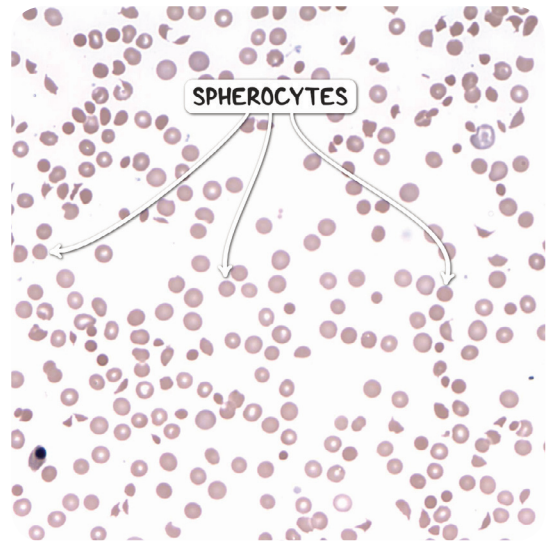


Figure 54.2 A peripheral blood smear demonstrating sphere shaped erythrocytes in an individual with hereditary spherocytosis. The erythrocytes have lost their biconcave shape.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

osms.it/paroxysmal-nocturnal-hemoglobinuria

PATHOLOGY & CAUSES

- Inherited, X-linked **hematologic stem cell disorder** resulting in nocturnal hemolysis, hemolytic anemia, bone marrow failure, thrombosis

CAUSES

- Mutation of *PIGA* gene in hematopoietic stem cells
 - *PIGA* required for synthesis of glycosylphosphatidylinositol (GPI) protein on cell surface
 - GPI anchors glycoproteins on erythrocyte surface, protecting cell from lysis by attenuating activity of complement
- GPI protein absence or deficiency → ↑

susceptibility to complement activity
→ complement-mediated intravascular hemolysis

- Three phenotypes of RBCs categorized according to amount of GPI-anchored proteins on cell surface
 - **Type I:** normal
 - **Type II:** decreased
 - **Type III:** absent

RISK FACTORS

- Hemolysis in PNH cases increases in setting of increased complement activation
 - Infections
 - Surgery
 - Blood transfusions
 - Strenuous exercise
 - Excessive alcohol use

COMPLICATIONS

- Intravascular, extravascular hemolysis → anemia
- Consequences of hemoglobin-mediated nitric oxide scavenging
 - Intravascular hemolysis → free hemoglobin → ↑ consumption of nitric oxide → smooth muscle dystonia, vasospasm (abdominal pain, esophageal spasm, erectile dysfunction)
- Venous, arterial thrombosis
 - Multifactorial etiology related to proinflammatory complement activity, decreased availability of nitric oxide with resulting vasoconstriction, endothelial cell activation, associated platelet aggregation/clot formation
 - Hepatic vein thrombosis (Budd–Chiari syndrome) → hepatomegaly, jaundice, ascites, gastric and/or esophageal varices
 - Intestinal vein thrombosis → ischemic colitis
 - Cerebral vein thrombosis → headache, neurologic effects
- Microvascular hemolysis + iron deposits in renal tubules → chronic kidney disease
- Bone-marrow failure, aplastic anemia related to hematopoietic stem cell injury
- Eculizumab treatments associated with increased risk of life-threatening neisserial infections

SIGNS & SYMPTOMS

- Variable according to degree of GPI-anchored protein loss → hemolysis
- Intermittent episodes (paroxysms) of hemoglobinuria
 - Dark urine
 - Hemolysis during night
- Clinical manifestations of anemia; e.g. pallor, fatigue, exertional dyspnea

DIAGNOSIS

LAB RESULTS

- Range from normal to abnormal according to degree of GPI-anchored protein loss, resulting hemolysis
- **RBCs normal morphologically** (pancytopenia may be evident in setting of bone marrow failure)
- Occasional poikilocytosis, anisocytosis
- Normochromic
- Normal to extremely decreased serum hemoglobin
- Reticulocyte count ranges from normal to decreased
- Evidence of hemolysis
 - Elevated bilirubin
 - Decreased haptoglobin
 - Elevated LDH
- **Direct antiglobulin (DAT/Coombs) positive**
- Hemoglobinuria, hemosiderinuria

OTHER INTERVENTIONS

- Bone marrow examination may indicate hypocellularity
- Flow cytometry

TREATMENT

MEDICATIONS

- Eculizumab
 - **Monoclonal antibody**, reduces complement-mediated hemolysis
 - Vaccinate against *Neisseria meningitidis*
- Iron, folic acid supplements support erythropoiesis
- Therapeutic anticoagulation and/or thrombolysis, as indicated for thrombosis
- Immunosuppressive therapy if aplastic anemia present

SURGERY

- Allogeneic hematopoietic stem cell transplant

OTHER INTERVENTIONS

- Red blood cell transfusions as needed

PIRUVATE KINASE DEFICIENCY

osms.it/piruvate-kinase-deficiency

PATHOLOGY & CAUSES

- Hematological enzymopathy caused by **deficient pyruvate kinase**, resulting in chronic, premature hemolysis of RBCs, hyperactive erythropoiesis
- Inherited, autosomal recessive **mutation of (PK-LR) pyruvate kinase-LR** (liver-red cell) gene
 - Homozygous for single PK-LR mutation/ heterozygous for two mutations
- Hemolysis primarily extravascular (within spleen); intravascular hemolysis variable
- Pyruvate kinase
 - Tetramer enzyme, catalyzes transphosphorylation of phosphoenolpyruvate into pyruvate, ATP during glycolysis
 - Pyruvate kinase deficiency-related block in glycolysis → accumulation of 2,3-bisphosphoglycerate (2,3-BPG) → shifts oxyhemoglobin dissociation curve to right → improved oxygen delivery to tissues → better tolerance of hemolytic anemia

CAUSES

- Hemolytic mechanism is unclear; possibly
 - ATP deficiency
 - Apoptosis of erythroid progenitors in spleen (ineffective erythropoiesis)

RISK FACTORS

- Most common in white people of Northern European descent, Asian people of Chinese descent, genetically-isolated communities of Swiss/German descent

COMPLICATIONS

- Pigmented gallstone formation
- Iron overload-associated organ damage
- Megaloblastic anemia related to folate deficiency

- Accelerated hemolysis during pregnancy/ with oral contraceptive use
- Neonatal icterus/non-immune hydrops fetalis
- Transient aplastic crisis induced by infections (e.g. parvovirus B19)

SIGNS & SYMPTOMS

- Variable presentation ranging from compensated disease to transfusion-dependent anemia
- Anemic signs and symptoms
 - Pallor, shortness of breath, activity intolerance
- Jaundice, splenomegaly

DIAGNOSIS

LAB RESULTS

- Decreased RBC count, reticulocytosis
- Increased serum glycolytic 2,3-BPG
- Hemoglobinuria, hemosiderinuria
- Evidence of hemolytic anemia with one or both of
 - Low levels of erythrocytic PK enzymatic activity
 - PK-LR gene mutation
- Evidence of hemolysis
 - Elevated indirect bilirubin
 - Elevated lactate dehydrogenase (LDH)
 - Decreased haptoglobin

OTHER DIAGNOSTICS

- Clinical evidence of hemolysis
 - Jaundice, pigmented (bilirubin) gallstones

TREATMENT

SURGERY

- Splenectomy
 - Reduces hemolysis
- Allogeneic hematopoietic cell transplantation
 - May be curative

OTHER INTERVENTIONS

- RBC transfusions
 - Often chronic
- Chelation therapy
 - Reduces iron-related organ damage
- Folic acid supplementation
 - Supports erythropoiesis
- Phototherapy, exchange transfusion
 - Treats neonatal jaundice

SICKLE-CELL ANEMIA

osms.it/sickle-cell-anemia

PATHOLOGY & CAUSES

- Hemolytic anemia **caused by sickle-cell disease** (SCD)
- A group of inherited hemoglobinopathies caused by **point mutation of beta globin gene** → produces hemoglobin S (HbS)
- RBCs containing HbS tend to polymerize, deform into sickle/crescent-shaped forms when deoxygenated
 - **Triggers for deoxygenation:** cold, dehydration, insomnia, alcohol consumption, stressful situations, overexertion, hormonal changes
 - Deoxygenation may be idiopathic
- Sickled cells less deformable than normal RBCs
 - Decreased lifespan due to hemolysis

HbSA

- Sickle-cell trait/benign carrier state
 - Heterozygous for HbS + hemoglobin A (normal hemoglobin)

HbS beta thalassemia

- Heterozygous for HbS + one beta thalassemia gene

HbSD, HbSE, HbSO

- Rare
- Heterozygous for HbS + one other abnormal hemoglobin (D, E, or O)

COMPLICATIONS

- Affect all body systems
- Hematologic
 - Anemia related to **aplastic crisis** involving temporary arrest of erythropoiesis
- Pain
 - **Vaso-occlusion, tissue ischemia, infarction;** dactylitis (acute pain in small bones of hands/feet especially in children)
- Increased risk of infection
 - Related to hyposplenism/asplenism, decreased tissue perfusion
- Central nervous system
 - Ischemic/hemorrhagic stroke; transient ischemic attack, seizures

TYPES

HbSS

- Sickle-cell disease
 - Homozygous for HbS
 - Chronic hemolytic anemia

HbSC

- Milder form of sickle-cell disease
 - Heterozygous for HbS + abnormal hemoglobin C

- Cardiovascular
 - Myocardial infarction, dysrhythmias, cardiomyopathy, heart failure, venous thromboembolism, leg ulcers, sudden death
- Respiratory
 - Acute chest syndrome (fever, chest pain, hypoxemia, wheezing, cough, respiratory distress), pulmonary hypertension, disordered breathing during sleep with nocturnal hypoxemia
- Genitourinary, reproductive
 - Priapism, erectile dysfunction; pregnancy complications, fetal/neonatal or maternal (e.g. intrauterine growth restriction, fetal death, low birthweight; preeclampsia, thromboembolic events)
- Endocrine
 - Delayed growth, development
- Skeletal
 - Osteoporosis, bone infarction
- Sensory
 - Proliferative retinopathy, retinal detachment
- Systemic
 - Multiorgan failure related to ischemia and/or infarction

SIGNS & SYMPTOMS

- Mild to moderate anemia (e.g. fatigue, activity intolerance, exertional dyspnea)
- **Hypersplenism**
- Pain from acute vaso-occlusive crisis

DIAGNOSIS

- Findings variable depending on inheritance pattern, degree of hemolysis
- Pain indicates cell sickling, vaso-occlusion

LAB RESULTS

- Vaso-occlusion, hemolysis, splenic sequestration → decreased hemoglobin, hematocrit, RBC count
- Reticulocytosis
- Increased white blood cell (WBC) count
- Peripheral blood smear analysis

- Mostly normochromic, normocytic cells; polychromasia may be present secondary to reticulocytosis
- Sickled cells present in SCD but not sickle-cell trait
- Canoe-shaped (partially sickled) RBCs
- Howell Jolly bodies
 - **Related to hyposplenism**
- Normal-to-increased mean corpuscular volume (MCV)
- Target cells
- Diagnostic tests to determine organ damage (e.g. urinalysis → hematuria, albuminuria from renal papillary damage)
- Evidence of hemolysis
 - Elevated unconjugated bilirubin
 - Elevated lactate dehydrogenase (LDH)
 - Low haptoglobin
- Positive solubility test (Sickledex)
- **Hemoglobin electrophoresis** provides definitive diagnosis (90–95% HbS)

TREATMENT

- Prevent/reduce occurrence of crises (e.g. immunizations to prevent infection, manage stress, prevent deoxygenation)

MEDICATIONS

- Hydroxyurea
 - **Increases cell deformability**, decreases RBC endothelial adhesion, increases hemoglobin F levels; reduces sickling
- L-glutamine
 - Reduces sickling
- Pain management
 - Analgesics, adjunctive, non-pharmacological therapies

SURGERY

- Hematopoietic cell transplantation

OTHER INTERVENTIONS

- Blood transfusions
- Folic acid supplements
- Manage iron deficiency



Figure 54.3 A recoloured scanning electron micrograph demonstrating a sickled erythrocyte.

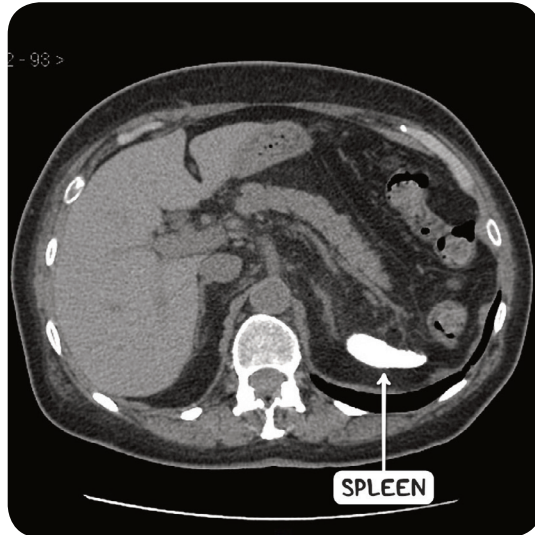


Figure 54.4 An abdominal CT scan in the axial plane demonstrating autosplenectomy in an individual with sickle cell disease. The splenic remnant is densely calcified.

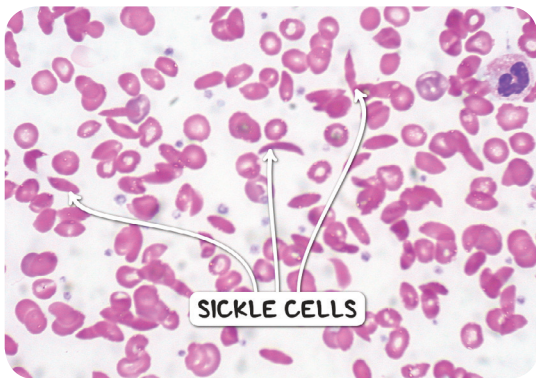


Figure 54.5 A peripheral blood smear containing sickled erythrocytes in an individual with sickle cell disease.